

ETW



Docket No.: 21901 US2 (C038435/0196414)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Roland JERMANN and Helmut LUTHER

Serial No.: 10/569,784

Filed: February 24, 2006

For: **USE OF BIOTIN OR A BIOTIN
DERIVATIVE FOR SKIN LIGHTENING
PURPOSES AND FOR THE
TREATMENT OF SENILE LENTIGINES**

Examiner: Not Yet Assigned

Art Unit: 1615

New York, New York
November 20, 2006

REQUEST FOR A CORRECTED FILING RECEIPT

Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants submit herewith this Request For A Corrected Filing Receipt in the above-captioned case. Attached is a copy of the Filing Receipt with the error noted thereon (**Exhibit A**).

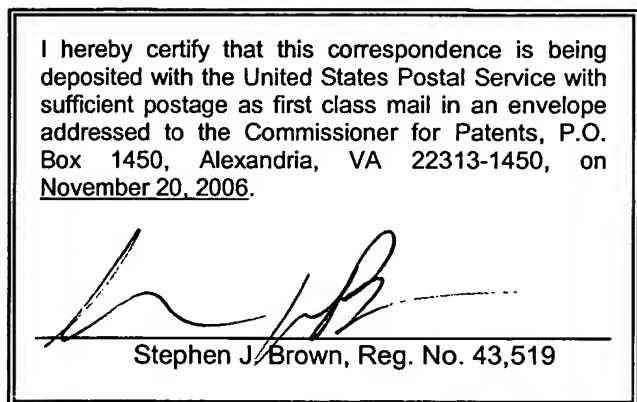
The error to be corrected is as follows:

The TITLE is incorrect. Therefore, please change the words "Use of biotin or a biotin derivative for lightening skin and treating age spots" to - - USE OF BIOTIN OR A BIOTIN DERIVATIVE FOR SKIN LIGHTENING PURPOSES AND FOR THE TREATMENT OF SENILE LENTIGINES - -.

Also enclosed are copies of the Transmittal Letter To The United States Designated/Elected Office (DO/EO/US) Concerning A Submission Under 35 U.S.C. 371 (**Exhibit B**); and a copy of the specification, claims, and abstract, as filed on February 24, 2006 (**Exhibit C**).


Applicants respectfully request the issuance of a corrected Filing Receipt in the above case.

It is not believed that any fee is required. If, however, it is determined that a fee is required, please charge such fee to Deposit Account No. 02-4467. A duplicate copy of this page is attached herewith.



Respectfully submitted,

By:



Stephen J. Brown
Registration No. 43,519
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300
Tel. (212) 541-2000
Fax (212) 541-4630

Also enclosed are copies of the Transmittal Letter To The United States Designated/Elected Office (DO/EO/US) Concerning A Submission Under 35 U.S.C. 371 (**Exhibit B**); and a copy of the specification, claims, and abstract, as filed on February 24, 2006 (**Exhibit C**).

Applicants respectfully request the issuance of a corrected Filing Receipt in the above case.

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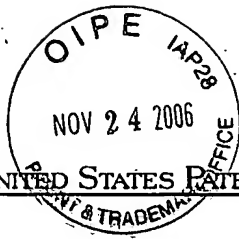
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on November 20, 2006.


Stephen J. Brown, Reg. No. 43,519

Respectfully submitted,

By: 

Stephen J. Brown
Registration No. 43,519
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300
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**ORIGINAL**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
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APPL NO.	FILING OR 371 (c) DATE	ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	DRAWINGS	TOT CLMS	IND CLMS
10/569,784	02/24/2006	1615	900	21901US(C038435/0196414)		18	1

CONFIRMATION NO. 6549

Stephen M Haracz
 Bryan Cave
 1290 Avenue of the Americas
 New York, NY 10104-3300

FILING RECEIPT

OC000000020888771

Date Mailed: 10/19/2006

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Roland Jermann, Laufen, SWITZERLAND;
 Helmut Luther, Grenzach-Wyhlen, GERMANY;

C38435 / 196414
 Dsm - DocId

26

Power of Attorney:

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1CH / Agr

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP04/09048 08/12/2004

Foreign Applications

EUROPEAN PATENT OFFICE (EPO) 03018730.6 08/26/2003

If Required, Foreign Filing License Granted: 10/18/2006

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US10/569,784**

Projected Publication Date: 01/25/2007

Non-Publication Request: No

Early Publication Request: No

Title *use of biotin or a biotin derivative for skin lightening purposes and for the treatment of senile lentigines*

Use of biotin or a biotin derivative for lightening skin and treating age spots

Preliminary Class

424

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER Title 35, United States Code, Section 184 Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted

under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).



UNITED STATES PATENT AND TRADEMARK OFFICE

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/569,784	Roland Jermann	21901US(C038435/0196414)

INTERNATIONAL APPLICATION NO.

PCT/EP04/09048

I.A. FILING DATE

PRIORITY DATE

08/12/2004

08/26/2003

Stephen M Haracz
 Bryan Cave
 1290 Avenue of the Americas
 New York, NY 10104-3300

CONFIRMATION NO. 6549

371 ACCEPTANCE LETTER



OC000000020888772

Date Mailed: 10/19/2006

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

02/24/200602/24/2006

DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and
 (c)(4) REQUIREMENTS

DATE OF COMPLETION OF ALL 35 U.S.C. 371
 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363). Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 02/24/2006
- Copy of the International Search Report filed on 02/24/2006
- Preliminary Amendments filed on 02/24/2006
- Information Disclosure Statements filed on 02/24/2006
- Oath or Declaration filed on 02/24/2006
- Request for Immediate Examination filed on 02/24/2006
- U.S. Basic National Fees filed on 02/24/2006
- Priority Documents filed on 02/24/2006
- Specification filed on 02/24/2006
- Claims filed on 02/24/2006
- Abstracts filed on 02/24/2006

C38435/196414
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 10/19/06
 ICC/H/B88

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

FREDERICK SMITH

Telephone: (703) 308-9140 EXT 210

PART 1 - ATTORNEY/APPLICANT COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER 21901 US (C038435/0196414) U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
INTERNATIONAL APPLICATION NO. PCT/EP2004/009048	INTERNATIONAL FILING DATE 12 August 2004	PRIORITY DATE CLAIMED 26 August 2003
TITLE OF INVENTION USE OF BIOTIN OR A BIOTIN DERIVATIVE FOR SKIN LIGHTENING PURPOSES AND FOR THE TREATMENT OF SENILE LENTIGINES		
APPLICANT(S) FOR DO/EO/US Roland JERMANN and Helmut LUTHER		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a submission under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a submission under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input checked="" type="checkbox"/> The US has been elected (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US): 6. <input checked="" type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input checked="" type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input checked="" type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input checked="" type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)). Items 11 to 20 below concern document(s) or information included: 11. <input checked="" type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A preliminary amendment. 14. <input type="checkbox"/> An Application Data Sheet under 37 CFR 1.76. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A power of attorney and/or change of address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 37 CFR 1.821- 1.825. 18. <input type="checkbox"/> A second copy of the published International Application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input checked="" type="checkbox"/> Other items or information: Certificate of Express Mailing (1 page); Return Postcard.		

This collection of information is required by 37 CFR 1.414 and 1.491-1.492. The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 15 minutes to complete, including gathering information, preparing, and submitting the completed form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)		INTERNATIONAL APPLICATION NO. PCT/EP2004/009048		ATTORNEY'S DOCKET NUMBER 21901 US (C038435/0196414)	
21. The following fees are submitted:				Applicant use	Office use only
<input checked="" type="checkbox"/> a) Basic national fee..... \$300.00				\$ 300.00	
<input checked="" type="checkbox"/> b) Examination fee..... \$200.00				\$ 200.00	
<input checked="" type="checkbox"/> c) Search fee..... \$500.00				\$ 500.00	
TOTAL OF ABOVE CALCULATIONS = \$1000.00				\$ 1,000.00	
<input type="checkbox"/> Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is \$250 for each additional 50 sheets of paper or fraction thereof.					
Total Sheets	Extra sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE		
21 - 100 =	0 /50 =	0	x \$250.00	\$ 0.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	19 - 20 =	0	x \$50.00	\$ 0.00	
Independent claims	2 - 3 =	0	x \$200.00	\$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$360.00	\$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				\$ 1,000.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				\$ 0.00	
SUBTOTAL =				\$ 1,000.00	
Processing fee of \$130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$ 0.00	
TOTAL NATIONAL FEE =				\$ 1,000.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property				\$ 0.00	
TOTAL FEES ENCLOSED =				\$ 1,000.00	
Amount to be refunded:					\$
Amount to be charged					\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>1,000.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ <u>1,000.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>02-4467</u> . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.					
NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.					
SEND ALL CORRESPONDENCE TO: Stephen M. Haracz, Esq. BRYAN CAVE LLP 1290 Avenue of the Americas New York, New York 10104 Phone: (212) 541-2000 Fax: (212) 541-4630					
				SIGNATURE	
				NAME	Stephen J. Brown
				REGISTRATION NUMBER	43,519

USE OF BIOTIN OR A BIOTIN DERIVATIVE FOR SKIN LIGHTENING PURPOSES AND FOR THE TREATMENT OF SENILE LENTIGINES

The present invention relates to the use of biotin or a biotin derivative alone, preferably with vitamin C or a vitamin C derivative, for the preparation of a pharmaceutical composition or a cosmetic composition for the treatment of senile lentigines, for smoothening skin color irregularities and/or for lightening natural skin color.

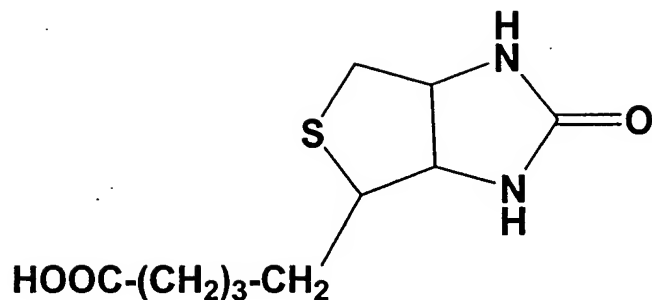
Senile lentigines are dark spots on the skin arising from the aging of the skin. They are a consequence of various aging processes, which are accelerated by incident light radiation. The skin thus appears inhomogeneous with respect to its color.

Tanning is a natural protective function of the skin with varying degrees of distinction in different ethnic groups. In many cultural circles a light skin tone is considered attractive so that a need for lightening the natural skin color arises.

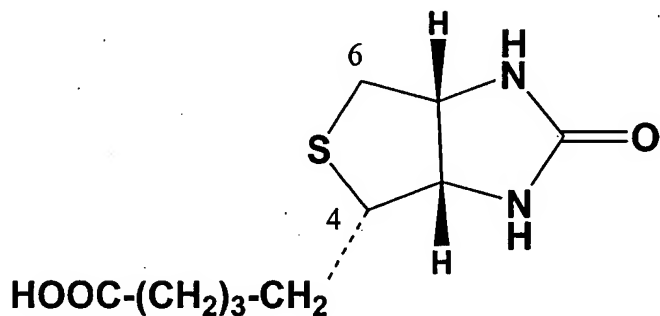
Compositions for skin lightening purposes are known, such as e.g. hydroquinone, kojic acid, arbutin, vitamin C as well as various plant extracts. One problem with many compositions, however, is that apart from a lightening of the skin or an elimination of the senile lentigos (liver spots, senile lentigines) also side effects such as e.g. skin irritations can occur. Plant extracts that lead to fewer skin irritations are generally not sufficiently effective.

There is a need for additional compositions, particularly cosmetic compositions that are well tolerated by the skin and yet are effective for skin lightening, for the treatment of senile lentigines and for smoothening skin color irregularities. The compositions should be at least as effective, preferably more effective than the familiar skin lightening compositions.

Biotin is a known active ingredient, which can be found in numerous cosmetic formulations and pharmaceutical compositions. Biotin is a compound of the following formula:



that can occur in eight different stereoisomeric forms. Biotin is in particular the D-(+)-biotin, i.e. the compound (3aS, 4S, 6aR)-2-oxohexahydrothieno[3,4-d]imidazole-4-valeric acid of the following formula:

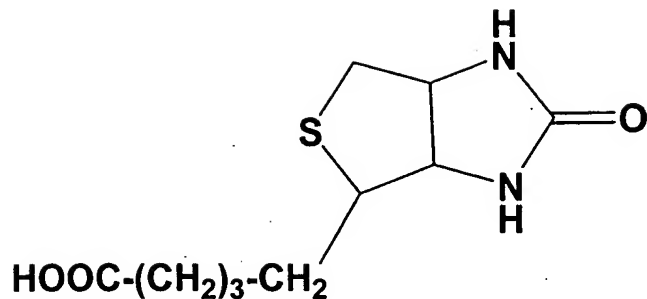


The effectiveness of the use of biotin in skin lightening applications has not been known until now.

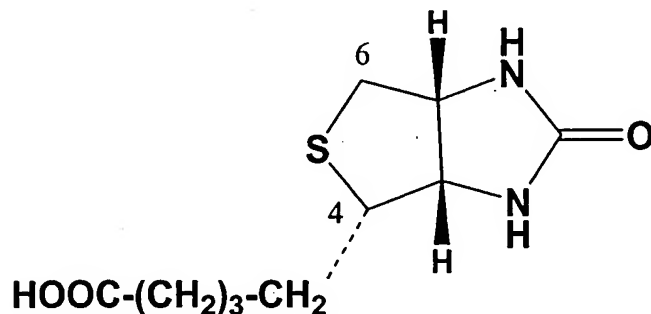
Pursuant to the invention it was surprisingly found that biotin exhibits a skin-lightening effect and thus can be used for the treatment of senile lentigos, for smoothening skin color irregularities as well as for lightening the natural skin tone.

The invention hence makes the use of biotin available for the preparation of a composition for lightening the natural skin tone, for smoothening skin color irregularities and/or for treating senile lentigines.

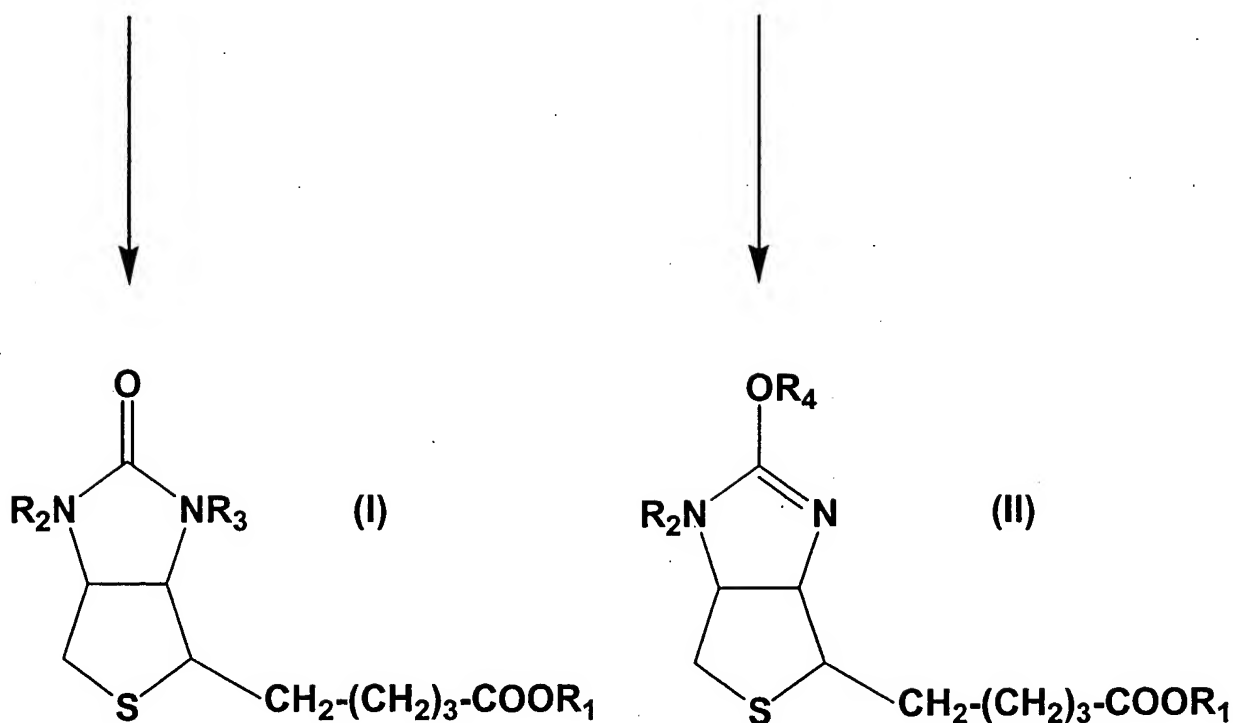
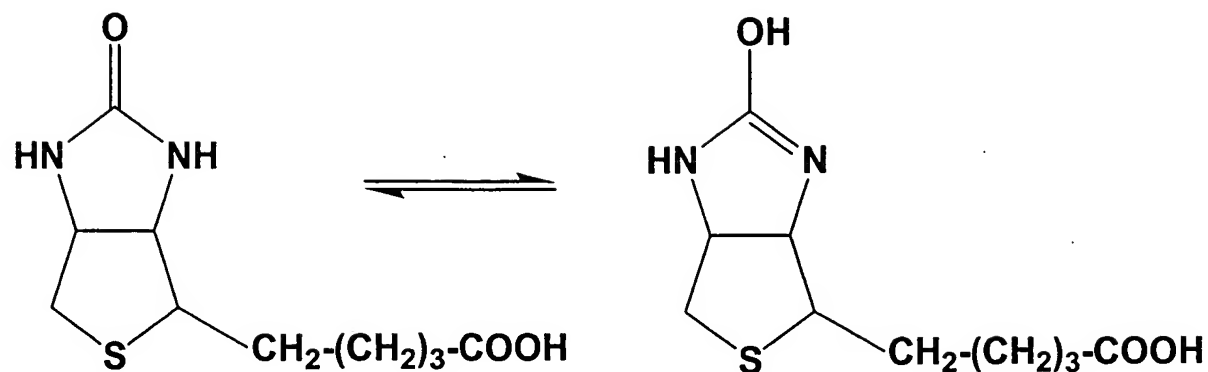
The term "biotin" pursuant to the invention relates to the eight stereoisomers of the formula:



either in a stereochemically pure form or as any random mixture of two or more stereoisomers. Particularly preferred pursuant to the invention is the D-(+)-biotin of the formula:



Biotin derivatives are known to the expert. These are compounds that are converted into biotin *in vitro*, particularly however *in vivo*. Lipophilic biotin derivatives, which generally penetrate the skin better than biotin itself, yet achieve equivalent effects as biotin, are particularly preferred. Apart from biotin, pursuant to the invention also biotin esters are particularly preferred, from which after penetration through the stratum corneum biotin is released again by the skin's own enzyme systems. Particularly preferred pursuant to the invention are biotin esters of the formulas I and II, which are deduced from biotin as follows:



wherein

R_1 = H, C_1 - C_{20} -alkyl, C_5 - C_7 -cycloalkyl, aryl;

R_2 and R_3 = independent from each other H, C_1 - C_5 -alkoxycarbonyl; and

R_4 = H, C_1 - C_{20} -alkyl, C_1 - C_5 -alkoxycarbonyl.

A C_1 - C_{20} -alkyl radical is preferably a C_1 - C_{10} -alkyl radical, even more preferred a C_1 - C_6 -alkyl radical such as a methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert.-butyl or an iso-butyl group.

A C_5 - C_7 -cycloalkyl radical is preferably a cyclohexyl group.

An aryl radical is preferably a C₅-C₁₀-aryl radical, in particular a phenyl group.

A C₁-C₅-alkoxycarbonyl radical is preferably a C₁-C₃-alkoxycarbonyl radical.

The radical R₁ is preferably a hydrogen atom or a C₁-C₆-alkyl radical.

At least one of the radicals R₂ or R₃ is preferably a hydrogen atom, even more preferred both radicals R₂ and R₃ are hydrogen atoms. The radical R₄ is preferably a hydrogen atom or a C₁-C₆-alkyl radical, even more preferred a hydrogen atom.

The radicals R₂, R₃ and R₄ are particularly preferred all hydrogen atoms, and the radical R₁ is a C₁-C₆-alkyl radical, as defined above.

Among the biotin derivatives, all stereoisomeric forms and salts are included pursuant to the invention either alone or in random mixtures.

Pursuant to the invention, biotin and the derivatives thereof can be used individually, however it is also possible to employ a mixture of biotin and one or more of its derivatives, for example biotin in a mixture with one or more biotin esters, as defined above. Likewise various biotin derivatives can be employed in mixtures with each other.

The preparation of biotin derivatives is known to the expert, and in this respect conventional standard methods of organic chemistry can be used, e.g. the esterification of biotin with the desired alcohol such as methanol or ethanol by splitting off water.

The biotin and the biotin derivatives can likewise be used in the salt form. Suitable biotin salts are not particularly limited, and in this context salts with alkalis, alkaline earths and other suitable metals, but also with ammonium and organic bases, especially sodium, potassium, calcium and magnesium salts, can be mentioned. Due to the nitrogen atoms, the biotin and especially also the biotin derivatives can exist also in the form of an acid addition salt upon reaction with a suitable acid, such as an inorganic or organic acid, especially a mineral acid, e.g. with HCl. The hydrochloride salt is particularly preferred. Preparation of the salts occurs in

the familiar fashion e.g. through reaction of the biotin or a derivative thereof with the corresponding base (e.g. NaOH or KOH) or the corresponding acid (e.g. HCl).

To the extent that within this description a "composition" is mentioned without more detailed specification, it should be understood both as a cosmetic composition and a pharmaceutical composition. To differentiate between cosmetic compositions and pharmaceutical compositions please refer e.g. to Römpp, Chemical Encyclopedia, 10th Edition and the literature cited therein. Pursuant to the invention biotin is preferably used for the production of a cosmetic composition in which the biotin is formulated together with additives that are compatible with cosmetics. Pursuant to the invention it is, however, also possible to use biotin for the production of a pharmaceutical composition, wherein the biotin is formulated with additives that are compatible with drugs. To the extent that within the framework of this application no other explanations are provided, the additives that are mentioned are additives that are compatible with cosmetics as well as additives that are compatible with drugs.

Pursuant to the invention, the compositions into which biotin is formulated are preferably topical compositions, such as e.g. liquid or solid oil-in-water emulsions, water-in-oil emulsions, multiple emulsions, micro-emulsions, PIT emulsions, Bickering emulsions, hydrogels, alcoholic gels, lipo-gels, single- or multiple-phase solutions, foams, ointments, plasters, suspensions, powders, creams, cleansers, soaps and other conventional compositions, which can also be applied e.g. by means of sticks, masks or as sprays.

The topical compositions preferably contain one or more additives, such as, for example, carriers and/or supplementary or auxiliary agents that are compatible with cosmetic and/or pharmaceutical compositions, as they are generally used in such preparations. Here for example fats, oils, waxes, silicones, emulsifiers, alcohols, polyhydric alcohols, thickening agents, moistening and/or moisture-retaining substances, surfactants, softening agents, foam-retarding agents, anionic, cationic, non-ionic or amphoteric polymers, alkanization or acidification agents, water softeners, adsorbents, sun-screen agents, electrolytes, sequestering agents, water, organic solvents, preservatives, bactericides, anti-oxidants, vitamins, scents, aromas, sweetening agents, colorants and pigments can be mentioned.

The topical formulations pursuant to the invention preferably contain one or more conventional fatty substances as additives, e.g., vegetable oils, liquid paraffin oils, isoparaffin oils, synthetic hydrocarbons, di-n-alkyl esters, fatty acids, fatty alcohols, ester oils, hydroxy-carboxylic acid esters, di-carboxylic acid esters, diol esters, symmetrical, non-symmetrical or cyclic esters or carbonic acid esters with fatty alcohols, mono-, di- and tri-fatty acid esters with glycerin, waxes and silicon compounds.

The fatty substances are generally present in the topical composition in a quantity of 0.1 to 50% by weight, preferably from 0.1 to 20% by weight, in particular from 0.1 to 15% by weight (in relation to the entire composition, respectively).

The topical compositions can contain other additives, such as, for example, one or more surface-active substances as emulsifying or dispersing agents. Suitable examples of such emulsifying or dispersing agents are known.

The emulsifying agents can be present in the topical compositions for example in parts from 0.1 to 25% by weight, preferred from 0.5 to 15% by weight, in relation to the entire composition.

The topical compositions can likewise contain conventional sun-screen agents as additives, for example conventional UV-A and/or UV-B filters. An overview of conventional UV-A and UV-B filters, which can also be employed in the compositions pursuant to the invention, can be found for example in EP-A 1 081 140. Pursuant to the invention of course also novel sun protection filters that are disclosed in this document for the first time can be used in the inventive compositions.

Suitable organic, mineral or modified mineral sun-screen filters are also disclosed in WO 01/64177, to which we refer here as well.

If desired, the inventive compositions can also contain protein hydrolyzates or derivatives thereof as well as suitable mono-, oligo- or poly-saccharides or their derivatives, as additives, as they are e.g. revealed in WO 01/64177. Further suitable additives and auxiliary agents, such as vitamins, pro-vitamins and vitamin precursors, allantoin, bisabolol, anti-oxidants, ceramides and pseudo-ceramides, triterpenes, monomer catechines, thickening agents, plant glycosides,

structure-providing substances (structuring agents), dimethylisosorbide, solvents, swelling and penetration adjuvants, perfume oils, pigments and colorants for dyeing the composition, substances for adjusting the pH value, complexing agents, opacifiers, pearly luster substances, expanding agents, film-forming, emulsion-stabilizing, thickening or adhesive polymers, especially cationic, anionic as well as non-ionic polymers are likewise revealed in WO 01/64177, which is incorporated herein by reference in so far.

The compositions are preferably formulated such that they are suitable for topical applications. Topical application occurs preferably at least once a day, e.g. two or three times a day. The treatment duration generally lasts at least two days until the desired effect has been achieved. The treatment duration can also take several weeks or months.

The quantity of the composition that is to be applied depends on the concentration of the active ingredient in the composition as well as the severity of the disease that is to be treated and/or the desired cosmetic success. In the case of a pharmaceutical usage generally the quantity of the active ingredient to be used per application is higher than in the case of a cosmetic use. An effective amount for the application depends on the condition of the skin, the person to be treated as well as the severity and type of the skin discoloration to be treated and other factors, which are known to the attending physician or cosmetician. For example application can occur such that a cream is applied to the skin. A cream is usually applied in a suitable quantity of 2 mg cream/cm² skin. The applied quantity however is not critical, and if no treatment success should be achieved with a certain quantity of the applied active ingredient then the applied amount can certainly be increased, for example by using topical formulations with higher concentrations.

Pursuant to the invention the active ingredient can be formulated as such or also in encapsulated form, for example in liposomal form. Liposomes are beneficially formed with lecithins without or with the addition of sterols or phytosterols. The encapsulation of the active ingredient can occur alone or together with other active ingredients.

The inventive composition contains a suitable quantity of 0.0001% by weight to approximately 50% by weight of biotin in relation to the total weight of composition. It is more preferred if biotin is present in a suitable quantity of 0.01% by weight to about 20% by weight, even more

preferred in a suitable quantity of about 0.01% by weight to about 1% by weight, in particular in a suitable quantity of about 0.1% by weight in relation to the total weight of the composition.

With respect to the type and preparation of the topical compositions as well as the disclosure of exemplary additives, we would like to refer to relevant literature, e.g. to NOWAK G.A., *Cosmetic Preparations – Volume 2, Cosmetic Preparations – Recipes, Starting Substances, Scientific Basis* (Verlag für chem. Industrie H. Ziolkowsky KG, Augsburg, Germany).

It is likewise possible to formulate biotin as an oral composition, for example in form of pills, tablets, capsules, which e.g. contain a granule or pellet, as liquid oral formulations or as an additive to foods, which is known to the expert in principle. Suitable methods and additives, with which the orally administered compositions can be produced pursuant to the invention, are disclosed e.g. in the standard work "Remington: The Science and Practice of Pharmacy", Lippincott, Williams and Wilking (Publisher) 2000, which is incorporated herein by reference.

Traditional excipients such as micro-crystalline cellulose, sodium citrate, calcium carbonate, disodium or dipotassium phosphate, sodium or potassium phosphate, glycine, agents to promote breakdown such as starch or alginic acid, binding agents such as polyvinylpyrrolidone, saccharose, gelatin or acacia gum, slip additives such as magnesium stearate, sodium lauryl sulfate or talcum can be used in tablet production as conventional additives for oral compositions, especially for tablets. If the composition is filled in gel capsules, conventional auxiliary agents for the production of granules are lactose or milk sugar as well as polyethylene glycols with a high molecular weight. Further additives for other oral formulations, and in particular for the formulation as additives to foodstuffs, are known to the expert, and we refer to the relevant literature, e.g. "Principles of Food Engineering" (Grundzüge der Lebensmitteltechnik), Horst-Dieter Tscheuschner (publisher), 2nd, newly revised Edition Hamburg: Behr's 1996.

In case of an oral composition, the content of the active ingredient (i.e. the biotin and/or biotin derivative) in the composition is generally 1% to 90%, preferably 10% to 80%, e.g. 50% or more. Administration occurs such that the desired effect is achieved and depends on the condition of the patient, the type and severity of the skin discoloration to be treated, etc. and

can easily be determined by the expert. A common daily dosage of the active ingredient is in the range from 0.1 µg/day to 50 mg/day, e.g. 20 µg/day to 2 mg/day.

Pursuant to the invention it was furthermore surprisingly found that apart from its own effectiveness for skin lightening purposes biotin exhibits a surprisingly high skin-lightening effect when it is administered together with vitamin C or a vitamin C derivative.

Vitamin C derivatives are known, and pursuant to the invention they are interpreted as all compounds that release vitamin C *in vivo* or *in vitro*, as well as solvates, hydrates and salts thereof. As examples of vitamin C derivatives e.g. glucosides of ascorbic acid and phosphates of ascorbic acid and in particular magnesium ascorbyl phosphate, sodium ascorbyl phosphate, calcium ascorbyl phosphate, potassium ascorbyl phosphate and mixed salts, such as e.g. sodium magnesium ascorbyl phosphate or sodium calcium ascorbyl phosphate, can be mentioned. Especially the phosphates frequently exist as hydrates, wherein the dihydrate form is the most common. Biotin is particularly preferred pursuant to the invention together with sodium ascorbyl phosphate, and the most preferred in form of the dihydrate, as it is available for example from Roche Vitamins AG under the product name STAY-C 50.

It has been known that vitamin C exhibits a skin-lightening effect, yet it was not known that a combination of biotin and vitamin C and/or a vitamin C derivatives have a skin-lightening effect that is considerably more distinct than the skin-lightening effect of vitamin C alone.

Pursuant to the invention the vitamin C and/or the derivatives thereof can be incorporated in the same formulation in which also the biotin is present. Vitamin C and/or the derivative thereof in a topical composition is preferably used in a quantity of 0.001% by weight to about 50% by weight in relation to the total weight of the composition. It is more preferred if vitamin C and/or the derivative thereof is used in a topical composition in a quantity of 0.01% by weight to about 20% by weight, even more preferred in a quantity of about 0.1% by weight to about 15% by weight, e.g. 1 to about 5% by weight, such as e.g. 3% by weight, in relation to the overall weight of the composition. With respect to the quantity of vitamin C and/or the derivative thereof in an oral composition we would like to refer to the aforementioned explanations of biotin which also applies to the quantity and dosage of vitamin C and/or the derivative thereof.

Pursuant to the invention, the term "composition" also includes an embodiment in which the composition is present in two separate parts, wherein one part contains the active ingredient biotin and the other part the active ingredient vitamin C or a derivative thereof. The two separate parts of the composition can each be topically applied or orally ingested, yet it is also possible that one separate part of the composition is applied topically and the other part of the composition is administered orally so that in the inventive composition e.g. one separate part contains the active ingredient biotin and is applied topically, while the other separate part contains the active ingredient vitamin C or a derivative thereof and is administered orally or wherein the separate part of the composition that contains the active ingredient biotin is administered orally and the separate part of the composition that contains the active ingredient vitamin C and/or a derivative thereof is applied topically.

For the preparation of the separate parts of the composition, the additives, active ingredients and the quantities of the respective additives and active ingredients contained in the separate parts, reference can be made to the aforementioned examples of topical and oral formulations with biotin, which also apply to the inventive embodiment in which the composition exists in two separate parts, each containing an active substance. For the quantity of vitamin C and/or the derivative thereof in one of the separate parts, reference can be made to the aforementioned embodiments wherein the composition is not present in the form of two separate parts, but where both active ingredients are present in a single composition.

To the extent that the composition contains both biotin and vitamin C and/or a derivative thereof, the weight ratio of vitamin C and/or the derivative thereof to biotin is preferably 500:1 to 1:500, more preferred 100:1 to 1:100, and in particular 30:1 to 1:30. It is furthermore preferred that the quantity of vitamin C and/or the derivative thereof is higher in the composition than the quantity of biotin. The information above applies both to embodiments in which biotin and vitamin C and/or a derivative thereof are present together in the mixture and to embodiments in which the composition consists of two separate parts, wherein the one part contains the active ingredient biotin and the other part the active ingredient vitamin C and/or a derivative thereof.

To the extent that the active ingredients mentioned here can be present as hydrates or solvates, the hydrates and solvates are also included in the present invention.

Pursuant to the invention a composition that contains both active ingredients together in a mixture is preferred, particularly preferred is a composition that is administered topically.

The following examples are provided to further illustrate the process of the present invention.

1. Formulation Example

A cream was produced in the familiar fashion from the following components:

	<u>Ingredients</u>	<u>INCI Description</u>	<u>%</u>
	<u>w/w</u>		
A)	Brij 721	Steareth 21	4.00
	Brij 72	Steareth 2	2.00
	Lanette O	Cetearyl Alcohol	2.00
	Glyceryl Myristate	Glyceryl Myristate	3.00
	Oleic Acid	Oleic Acid	6.00
	Tegosoft M	Isopropyl Myristate	3.00
	Estol 1517	Isopropyl Palmitate	3.00
	Transcutol CG	Ethoxydiglycol	5.00
	Phenonip	Phenoxyethanol & Methylparaben & Ethylparaben & Propylparaben & Butylparaben	0.80
	Dow Corning 200, 350 cs	Dimethicone	0.50
	BHT	Butylated Hydroxytoluene	0.05
B)	Deionized water	Aqua	Ad
100			
	Propylene Glycol	Propylene Glycol	5.00
	Edeta BD	Disodium EDTA	0.10
	Keltrol T	Xanthan Gum	0.20
	Carbopol ETD 2001	Carbomer	0.30

C)	TEA 99%	Triethanolamine	qs pH
7			
	Biotin	Biotin	0.10
	Deionized water	Aqua	10.00
D)	Deionized water	Aqua	6.00
	STAY-C 50	Sodium Ascorbyl Phosphate	3.00

Parts A) and B) were heated separately from each other to 75°C, respectively, while stirring. As soon as parts A) and B) were homogeneous, part B) was added to part A) while stirring. The mixture was homogenized at 11,000 RPM for 30 seconds. Part C) was pre-warmed to 65°C and added to the homogenized mixture of A) and B). The mixture of A), B) and C) was cooled down to 40°C, and part D) was added. The mixture was cooled down to the ambient temperature (25°C) while stirring.

The resulting cream had a pH value of 7.0 and had a viscosity (Brookfield RVT, 25°C, Spindle 5, 10 RPM) of approximately 20,000 cP.

Apart from a cream pursuant to the invention, a placebo was produced correspondingly, in which neither sodium ascorbyl phosphate nor biotin were present, as well as a cream with 0.1% biotin exclusively and a cream with 3% sodium ascorbyl phosphate exclusively.

2. Test Example

39 female subjects were divided into three groups of 13 persons each. The subjects applied twice a day for three months a test formulation on the left and a second test formulation on the right halves of their faces as well as on the left and the right backs of their hands. The test formulations were coded and corresponded to a placebo formulation and a formulation with the desired test substance. The three groups hereby tested the creams produced above with 3% sodium ascorbyl phosphate (STAY-C 50), 0.1% biotin and with a mixture of 3% sodium ascorbyl phosphate and 0.1% biotin.

A CR 300 chromometer was used to measure the lightening of the senile lentigines. The values that were obtained were provided as ITA° values. ITA° describes the pigmentation degree of the skin and/or the senile lentigines. The values reflected below correspond to the differences in ITA° values over the base line before start of the study. The higher the value, the greater the lightening of the skin. The ITA° values were determined after 29, 57 and 85 days, i.e. after approximately one month, after about two months and after about three months. The results are shown in the following table.

Composition	ITA°			ITA°-p-values		
	Day 29	Day 57	Day 85	Day 29	Day 57	Day 85
Placebo	1.53	7.67	9.29	0.381	0.953	0.857
3% NAP	4.46	7.53	8.80			
Placebo	2.75	5.93	8.07	0.156	0.480	0.217
0.1% Biotin	5.57	7.55	11.16			
Placebo	3.32	6.89	9.70	0.055	0.006	0.045
3% NAP + 0.1% Biotin	7.16	11.65	13.42			

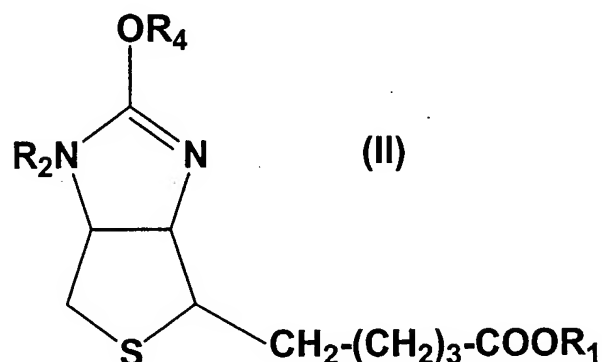
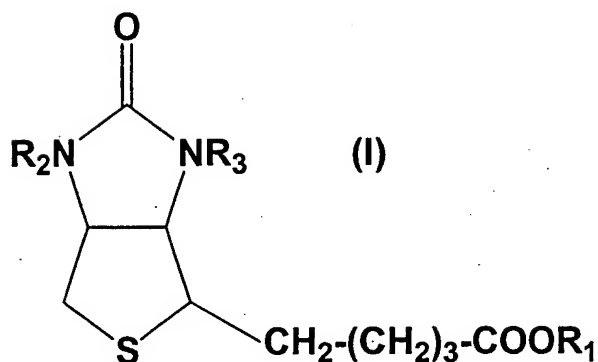
The study was conducted during the winter months, and during this time the skin lightens naturally. This explains why also the placebo formulations led to a slight skin lightening. The skin lightening effect for the placebo formulations however is only small.

Surprisingly biotin had a skin lightening effect already at a concentration of 0.1%, which is greater after one and three months and about as high as that of the known skin lightening composition vitamin C after two months. The very high skin lightening effect of a mixture of 3% sodium ascorbyl phosphate and 0.1% biotin was particularly surprising.

The results of the study are shown in Figures 1 through 3.

CLAIMS:

1. Use of biotin, a biotin derivative or a salt thereof for manufacturing a composition for lightening the skin, smoothening skin color irregularities and/or treating senile lentigos.
2. Use according to claim 1, wherein the biotin salt is an alkali salt, an earth alkali salt, an ammonium salt or a hydrochloride of the biotin or the biotin derivative.
3. Use according to claim 1 or 2, wherein the biotin derivative is a compound of formula I or formula II:



wherein

R₁ is H, C₁-C₂₀-alkyl, C₅-C₇-cycloalkyl, or aryl;

R₂ and R₃ are each independently H or C₁-C₅-alkoxycarbonyl; and

R₄ is H, C₁-C₂₀-alkyl or C₁-C₅-alkoxycarbonyl.

4. Use according to any of claims 1 to 3, wherein the composition is for topical administration.
5. Use according to any of claims 1 to 3, wherein the composition is for oral administration.

6. Use according to any of claims 1 to 5, wherein the composition is a cosmetic composition.
7. Use according to any of claims 1 to 5, wherein the composition is a pharmaceutical composition.
8. Use according to any of claims 1 to 7, wherein the biotin, the biotin derivative or the salt thereof is present at a concentration of 0.001 to 50% by weight, in relation to the weight of the composition.
9. Use according to claim 8, wherein the biotin, the biotin derivative or the salt thereof is present at a concentration of 0.01 to 1% by weight, in relation to the weight of the composition.
10. Use according to any of claims 1 to 9, wherein the biotin, the biotin derivative or the salt thereof are used together with vitamin C or a vitamin C derivative.
11. Use according to claim 10, wherein the biotin, the biotin derivative or the salt thereof is used together with sodium ascorbyl phosphate or a hydrate thereof, in particular the dihydrate thereof.
12. Use according to claim 10 or 11, wherein the vitamin C or the vitamin C derivative is present at a concentration of 0.001 to 50% by weight, in relation to the weight of the composition.
13. Use according to claim 12, wherein the vitamin C or the vitamin C derivative is present at a concentration of 0.1 to 15% by weight, in relation to the weight of the composition.
14. Use according to any of claims 9 to 13, wherein the weight ratio of the vitamin C or the vitamin C derivative, respectively, to the biotin, the biotin derivative or the salt thereof is 500:1 to 1:500.

15. Use according to claim 14, wherein the weight ratio of the vitamin C or the vitamin C derivative, respectively, to the biotin, the biotin derivative or the salt thereof is 30:1 to 1:30.
16. Use according to any of claims 9 to 15, wherein the composition is arranged such that the biotin, the biotin derivative or the salt thereof and the vitamin C or the vitamin C derivative, respectively, are physically separated.
17. Use according to claim 16, wherein one of the active ingredients is formulated for oral administration and the other is formulated for topical administration.

ABSTRACT

The present invention relates to the use of biotin alone, preferably, however, with vitamin C or a derivative thereof, for the preparation of a cosmetic composition or of a pharmaceutical composition for skin-lightening purposes, for the elimination of skin color irregularities and for the treatment of senile lentigines.